American Journal of Hematology 64:73–75 (2000)

Autoimmune Thyroid Disease and Antiphospholipid Antibodies

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Objective: **Autoimmune thyroid disease (ATD) is associated with circulating autoantibodies reactive with epitopes on thyroid tissue and that are thought to be pathogenic in the development of these diseases. Antiphospholipid antibodies (APLA) are a family of immunoglobulins that recognize a variety of plasma proteins in association with anionic phospholipids. These antibodies may lead to a number of clinical syndromes including venous and arterial thromboses, thrombocytopaenia, and recurrent fetal loss. We have studied the prevalence of APLA in patients with ATD and have determined the prevalence of the APLA syndrome among APLA-positive patients.** ***Design:*** **The study was a retrospective survey of patients with autoimmune thyroid disease attending the endocrinology clinic of a tertiary care academic hospital.** ***Patients and Measurements:*** **One hundred and thirty patients with autoimmune thyroid disease from the endocrinology clinic at our hospital were studied. 84% had chronic thyroiditis and 16% had Graves' disease. Free T4 and thyroid stimulating hormone (TSH) levels, antimicrosomal and antithyroglobulin antibodies, and an antiphospholipid antibody test were performed on all subjects.** ***Results:*** **43% of patients with chronic thyroiditis and 43% of patients with Graves' disease were APLA positive, with an overall rate of 43% APLA positivity among patients with ATD. Of the 56 patients that were APLA positive, forty-eight (86%) had APLA of the IgG subtype, four (7%) had IgM antibodies, and nine (16%) had both IgG and IgM antibodies. None of the patients had clinical evidence of the APLA syndrome.** ***Conclusions:*** **We conclude that the prevalence of APLA in ATD is increased compared to healthy individuals but that this is likely to be an epiphenomenon, However, prolonged follow up is necessary in order to determine the true clinical significance of these antibodies in ATD patients. Am. J. Hematol. 64:73–75, 2000.**

Key words: APLA; autoimmune thyroid disease; autoantibodies

Antiphospholipid antibodies are a family of immunoglobulins that recognize a variety of plasma proteins in association with anionic phospholipids [1]. These antibodies may be of the IgG, IgM, or IgA class and may lead to a number of clinical syndromes including venous and arterial thrombosis, thrombocytopaenia and recurrent fetal loss [2]. Patients with these clinical manifestations and persistently positive tests for antiphospholipid antibodies are designated as having the APLA syndrome. This syndrome may arise in the setting of an underlying autoimmune disease in particular systemic lupus erythematosus or may occur de novo in which case it is known as the primary antiphospholipid syndrome [3].

Autoimmune thyroid disease is associated with circulating autoantibodies that are reactive with epitopes on thyroid tissue and are thought to be pathogenic in the development of these diseases. However, other autoantibodies, including APLA, that are not thyroid specific have been detected in these patients [4]. The clinical significance of these antibodies is uncertain: some have reported that while patients with ATD may have circulating APLA they do not manifest any of the clinical abnormalities associated with the APLA syndrome while others have claimed that the presence of APLA may have clinical significance [5–7].

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Received for publication 19 October 1999; Accepted 1 December 1999

We recently encountered four patients with ATD in whom thromboembolic phenomena occurred. The evaluation of these patients included testing for the presence of APLA and in all of the patients an elevated titer of APLA was found. In these cases, considerable doubt existed regarding the significance of APLA in patients with ATD. An increased prevalence of APLA in this group of patients without a correspondingly high prevalence of thromboembolic events would imply that the presence of APLA can be attributed to non-tissue-specific antibody production in patients with an autoimmune disease. However, an increased prevalence of thromboembolic complications in these patients would suggest that the presence of APLA might confer a hypercoagulable state upon these patients.

In order to determine the prevalence of APLA among patients with ATD and to assess the relationship between the presence of the antibody and thromboembolic events, we have undertaken the current prospective study.

PATIENTS AND METHODS

One hundred and thirty patients with autoimmune thyroid disease from the endocrinology clinic at our hospital were studied. 122 patients were female and 8 were male. One hundred and nine patients (84%) had chronic thyroiditis, and twenty-one (16%) had Graves' disease. The patients were all evaluated for clinical signs of the antiphospholipid syndrome. Laboratory tests performed on all of the subjects were as follows: free T4 and thyroid stimulating hormone (TSH) levels, antimicrosomal and antithyroglobulin antibodies, and an antiphospholipid antibody test using an enzyme linked immunosorption assay (ELISA) (READS, USA). This antiphospholipid test system uses an ELISA plate coated with the antigens β-2-glycoprotein 1 and cardiolipin. The thyroid hormone and antibody studies were performed using standard laboratory assays.

Correlation between APLA levels and antimicrosomal antibody levels and APLA levels and antithyroglobulin levels were performed using the Spearman correlation test for non-parametric variables (GraphPad Prism version 2.0 software, San Diego, CA).

RESULTS

Forty-seven of the 109 patients (43%) with chronic thyroiditis were APLA positive. Likewise, 43% of patients (9 of 21) with Graves' disease were found to be APLA positive, with an overall rate of 43% APLA positive patients among the patients with ATD. For a patient to be considered to be APLA positive, two positive tests for the antibody performed 6 weeks apart were required.

Of the 56 patients in the study that were APLA positive, forty-eight (86%) had APLA of the IgG subtype, four (9%) had IgM antibodies, and nine (16%) had both IgG and IgM antibodies. No correlation was found between APLA titer and antithyroid antibody titer. None of the patients had clinical evidence of the APLA syndrome, namely, venous or arterial thromboembolism, thrombocytopaenia, or a history of recurrent fetal loss.

There was no correlation between APLA titer and antimicrosomal antibody titer ($P = 0.62$ by two-tailed Spearman correlation test for non-parametric variables). There was also no correlation between APLA titer and antithyroglobulin titer ($P = 0.85$ by two-tailed Spearman correlation test for non-parametric variables).

DISCUSSION

Antiphospholipid antibodies are often detected in patients with autoimmune diseases. In these patients the prevalence of a clinical syndrome attributable to the circulating antibodies is low and their presence is presumed to reflect the excessive stimulation of B lymphocyte clones with autoreactive potential [8]. This presumed stimulation results in the synthesis of a variety of non-organ-specific autoantibodies. However, the occurrence of this phenomenon leading to the formation of APLA in ATD is debated. Paggi found APLA in 17 of 31 patients with ATD [5]. The antibody titer was highest in patients with Graves' disease and decreased with methimazole treatment. Likewise, Marongiu found an increased incidence of APLA positivity in Graves' disease patients compared to healthy controls [6]. In these patients the antibody was of the IgG subtype. In contrast, Petri and coworkers were unable to replicate these results in a cohort of patients with Graves' disease and Hashimoto's thyoiditis and concluded that APLA is no more common in ATD than in healthy individuals [7].

The results of our study indicate that the prevalence of APLA is increased in patients with ATD. 43% of patients with Graves' disease and an identical percentage of patients with Hashimoto's thyroiditis had persistently elevated APLA titers. Most patients had IgG antibodies and in the majority the titer was only mildly or moderately increased. There was no correlation between the APLA titer and the titer of specific antithyroid antibodies. These findings support the notion that nonspecific autoantibody production may accompany the synthesis of tissue-specific immunoglobulin in autoimmune disease [9]. In the case of ATD, we propose that the production of antithyroglobulin and antimicrosomal antibodies is accompanied by the synthesis of APLA as an epiphenomenon. Furthermore, none of the 130 patients studied had clinical manifestations of the APLA syndrome, and only 4 patients with Graves' disease and 8 patients with chronic thyroiditis had APLA titers above 40 IgG units, a value that has been shown to have a predictive value for the occurrence of venous thrombo-

embolic events [10]. These findings further imply that the presence of these antibodies is likely to be related to "overstimulation" of autoreactive B cell clones.

In conclusion, our results suggest that patients with ATD need not be examined routinely for the presence of APLA. In patients in whom APLA has been detected and in whom no clinical evidence of the APLA syndrome is present, long-term follow-up is of interest in order to determine whether prolonged presence of the antibodies may result in the development of signs of the antiphospholipid syndrome.

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